**I. Review of the Drawings.** The Office Action Summary mailed July 15, 1997 did not include a Form PTO-948, Notice of Draftsperson's Patent Drawing Review, although twenty four figures were submitted with the application (see Filing Receipt for confirmation). Applicants request that the application be forwarded to the Draftsman for review and that a Form PTO-948 be issued.

**II. Applicant's Invention,**

The invention is directed to a method for treating a bone defect by introducing a poorly crystalline apatitic calcium phosphate at the defect site. The poorly crystalline apatitic calcium phosphate possesses desirable properties which are useful in the treatment of bone defects, namely, the implanted poorly crystalline apatitic calcium phosphate is strongly resorbable and bone is formed at the implant site. The poorly crystalline apatitic calcium phosphate is characterized in that it has a crystallinity similar to that of naturally occurring bone.

The invention is further directed to a method of treating a bone defect in which a hydrated precursor comprising amorphous calcium phosphate and a promoter is applied to a bone defect site. The promoter enhances the amorphous calcium phosphate into poorly crystalline apatitic calcium phosphate. The hydrated precursor is converted into a hardened poorly crystalline apatitic calcium phosphate at the implant site, where it is resorbed and bone is formed at the implant site.

**III. Amendments to the specification.**

The specification has been amended to correct typographical errors. The amendments are formal in nature and, as such, do not represent introduction of new matter.

**IV. Restriction requirement.**

The Examiner deems the above-identified application to contain claims directed to more than one invention. Applicants hereby confirm election of the invention of Group I, classified in class 606, subclass 76-77, directed to an implantation method. Claims 1-16 are directed to the elected invention.

**V. Rejection of claims 1-16 under 35 U.S.C. §112, second paragraph.**

Claims 1-16 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter applicants regard as the invention.

In particular, the Examiner questions the composition of a "poorly crystalline" apatitic calcium phosphate used in the method of the invention. Applicants submit that the term "poorly crystalline' has been fully defined in the specification, namely at page 7, lines 14-23. Applicants further submit that the term "poorly crystalline" is a term of art understood in the bone community. In particular, a "poorly crystalline" material (here, apatitic calcium phosphate) is a material in which the crystals are very small, e.g., on the order of nanometers. Due to the small crystal size, the material possesses a distinctive X-ray diffraction (XRD) pattern having only a few discernible, broad reflections. This X-ray diffraction pattern is similar to that of naturally occurring bone.

Third parties also have used the term to describe the crystalline state of naturally occurring bone. Glimcher in "Recent Studies of the Mineral Phase in Bone and Its Possible Linkage to the Organic Matrix by Protein-bound Phosphate Bonds" describes the mineral phase of bone thusly:

> [D]espite the fact that it has been known...for over 50 years that [the solid mineral phase of bone] has the X-ray structural characteristics of *poorly crystalline hydroxyapatite* (p.c.HA), no general agreement has been reach either about the details of its exact molecular structure or its chemical composition. In great part this stems from the fact that the quantitative characteristics of the *X-ray diffraction patterns generated by samples of bone tissue differ significantly from those generated by standard preparations of highly crystalline hydroxyapatite* (HA). Indeed, even mineral from the most mature bone generates only a few discernible reflections of hydroxyapatite and even those are quite broadened.
>
> Electron micrographs of bone, which have revealed *the very small of the bone crystals (about (15-35 Å) x (50-100 Å) x (400-500 Å)), help to explain this aspect of the X-ray diffraction pattern.* (*Phil. Trans. R. Soc. Lond. B* **304**:479 (1984), at page 480; emphasis added.)

Thus, a "poorly crystalline" material is recognized in the art as a material having a unique XRD pattern which is related to the small nanometer scale crystal size of the material. The specification further makes clear that "poorly crystalline apatitic calcium phosphate" used in the method of the invention has the X-ray diffraction pattern similar to naturally occurring bone. It

is submitted therefore that claim 1, as amended, defines the material in a manner to distinctly claim the subject matter of the invention and to render it distinguishable from prior art calcium phosphates.

The Examiner further submits that the *in vivo* conversion process is not described in terms of reactants, catalysts, components or conditions necessary to form the poorly crystalline apatitic calcium phosphate. Claim 2 has been amended state that the hydrated precursor comprises an amorphous calcium phosphate and a promoter and that the conversion process takes place at the implant site. Support for these amendments is found on page 18, line 23 - page 19, line 2. Thus claim 2 now sets forth the components of the hydrated precursor and the conditions of the conversion, namely those at the implant site. It is submitted that claim 2, as amended, clearly and distinctly claims subject matter applicant regards as the invention.

It is respectfully requested that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

**V. Rejection of the claims under 35 U.S.C. §103 over Chow or CA 113:218168j or CA 87:73954v.**

Claims 1-16 stand rejected under 35 U.S.C. §103 as being unpatentable over any of U.S. Patent No. 5,525,148 to Chow et al. ("Chow '148) or CA 113:218168j or CA 87:73954v. The Examiner does not consider the recited poorly crystalline amorphous calcium phosphate to be distinguishable over disclosed amorphous calcium phosphates of the art. Applicants respectfully traverse the rejection.

(a) Claim 1 and those claims dependent thereon. There is no teaching or suggestion in any of the cited documents of forming a *poorly crystalline* apatitic calcium phosphate, as is recited in claim 1 of the instant invention. A poorly crystalline apatitic calcium phosphate is defined in the specification and understood in the art to have nanoscale crystalline domains and to possess an XRD pattern similar to naturally occurring bone.

CA 87:73954v teaches the formation of amorphous calcium phosphate (ACP) by separation of a precipitate from a mother solution after various aging times. Its chemical and physical properties are reported as a function of aging time. ACP, by definition, is *amorphous*, that is, total lacking any crystallinity. Further, ACP does not possess nanoscale crystalline

domains or an XRD pattern similar to naturally occurring bone and hence the reference fails to teach or suggest the poorly crystalline calcium phosphate used in the method of the instant invention. In support of this statement, compare the XRD pattern of naturally occurring bone (Figure 1 of the above-identified application) with the XRD pattern of an amorphous calcium phosphate (Figure 3(a) of the above-identified application). Lastly, the reference does not teach or suggest application of the material to an implant site, as is recited in claim 1. Nor does the reference teach or suggest resorbability of the material at an implant site with the formation of bone.

CA 113:218168j teaches the formation of crystalline hydroxyapatite (HA) by reaction of $Ca(NO_3)_2$ and $(NH_4)_2HPO_4$ at various temperatures. Hydroxyapatite is a crystalline material which possesses large crystalline domains and which does not have an XRD pattern similar to naturally occurring bone. In support of this statement, the applicants direct the Examiner to Figure 2 of Glimcher (page 481) in which the X-ray diffraction patterns of an amorphous calcium phosphate (Figure 2(a)), a poorly crystalline hydroxy apatite (Figure 2(b)) and the X-ray diffraction pattern of crystalline hydroxyapatite (Figure 2(c)) are shown. Clearly, Glimcher considers these three materials to be separate and distinguishable. For example, note the substantial absence of any reflections in the XRD for amorphous calcium phosphate. In contrast, note the numerous sharp reflections in the XRD for HA. The sharpness of the peaks is an indication of the higher degree of crystallinity for HA as compared to the poorly crystalline apatitic calcium phosphate used in the method of the invention. Further, the reference does not teach or suggest application of the material to an implant site, as is recited in claim 1. Nor does the reference teach or suggest resorbability of the HA at an implant site with the formation of bone. In fact, HA is recognized in the art as being inert in biological environments.

Chow '148 discloses a self setting calcium phosphate cement used to prepare crystalline HA. HA is a highly crystalline material which does not possess the degree of crystallinity of naturally occurring bone, as is recited in claim 1 (note that crystalline HA is being formed by Chow, as is confirmed by the fact that product conversion is determined by observation of HA in the XRD pattern (see, col. 8, lines 22-31)). There is no teaching or suggestion in Chow '148 of a poorly crystalline apatitic calcium phosphate having a degree of crystallinity similar to naturally occurring bone.

Nor is there any teaching or suggestion of a strongly resorbable material, as is recited in claim 1. Chow '148 states that the hydroxyapatite crystallites formed as the cement sets resorb only slowly over time (col. 12, lines 27-32).

Nor would a combination of the cited references teach the claimed invention. Since none of the cited references teach or suggest the use of a poorly crystalline apatitic calcium phosphate having the recited properties in the treatment of bone defects, a combination of the references also fails to teach or suggest the claimed invention.

(b) Claim 2 and those claims dependent thereon. There is no teaching or suggestion in any of the cited references of a hydrated precursor comprised of an amorphous calcium phosphate and promoter, which is converted into a hardened poorly crystalline apatitic calcium phosphate at the implant site, as is recited in claim 2.

CA 87:73954v and CA 113:218168j disclose the formation of amorphous calcium phosphate (ACP) and crystalline hydroxyapatite (HA), respectively. There is no teaching or suggestion of combining an ACP with a promoter so as to form a self-setting material, which is capable of forming a hardened, poorly crystalline apatitic calcium phosphate at body temperature, physiological pH and in the presence of physiological fluid.

Chow '148 teaches a self-setting cement including calcium phosphate salts in a supersaturated phosphate solution and/or at a pH of greater than 12.5. The hardened product of Chow is "predominantly hydroxyapatite", which is a crystalline material (see Sec. V(a), above).

There is no teaching or suggestion in Chow '148 of a hydrated precursor which is comprised of an amorphous calcium phosphate and a promoter which forms a hardened poorly crystalline apatitic calcium phosphate at the implant site. In fact, Chow '148 admits that:

> a slurry of DCPD, DCPA, octacalcium phosphate (OCP), *amorphous calcium phosphate* (ACP), α-tricalcium phosphate (α-TCP), β-tricalcium phosphate (β-TCP), or a mixture of these salts does not produce a setting cement or act as an effective remineralizing agent. (col. 5, lines 55-59, Chow '148; emphasis added).

Chow teaches that the only way to obtain a setting cement for these materials is to combine them at high phosphate concentrations and/or high pH. Neither of these conditions are encountered "at the implant site", as is recited in claim 2 of the instant application.

Further, the reaction of an amorphous calcium phosphate, even at high phosphate

concentration or high pH, does not produce a hardened poorly crystalline apatitic calcium phosphate, as is recited in claim 2. Table 2 reports the results of reaction of ACP and $Ca(OH)_2$ at high phosphate concentrations (example 54) and at high pH (example 55). Neither of these two reactions leads to a "hardened" product, as indicated by the poor tensile strength of the resultant products (DTS of 0.014 and 0 Mpa, respectively).

Nor would a combination of the cited references teach the claimed invention. Since none of the cited references teach or suggest the use of a hydrated precursor having the recited properties in the treatment of bone defects, a combination of the references also fails to teach or suggest the claimed invention.

For the foregoing reasons, it is submitted that claims 1-16 are distinguishable from Chow '148, CA 113:218168j and CA 87:73954v, either alone or in combination. It is respectfully requested that the rejection be withdrawn.

**VI. Rejection of the claims under 35 U.S.C. §103 over Nagata et al. or Palmer et al. in view of Niwa et al.**

Claims 1-16 stand rejected under 35 U.S.C. §103 as being unpatentable over Nagata et al. ("Nagata") or Palmer et al. ("Palmer") in view of Niwa et al. ("Niwa"). Both Nagata and Palmer teach the formation of a highly crystalline hydroxyapatite in a two step process which involves (a) precipitation and collection of and ACP from a solution of calcium and phosphate ions; and (b) heat treating the ACP under conditions, e.g., hydrothermal conditions or high temperatures, which result in the formation of highly crystalline HA. The Examiner relies on Niwa to teach implantation of a material into bone defects.

The Examiner suggests that the procedures and materials used by Nagata or Palmer are equivalents to those described in the instant application and that the resultant products therefore are identical. Applicants respectfully traverse the rejection.

The procedures set forth by Nagata and Palmer are not equivalent to those set forth in the working examples of the instant application. The working examples of the instant invention all describe a method of making a poorly crystalline apatitic calcium phosphate by reaction of an ACP and a promoter at room temperature or body temperature. The specification makes clear that reaction at elevated temperatures is undesirable because of the negative effect such

]temperatures have on the crystallinity of the product calcium phosphate. See, page 3, lines 2-10. While it is true that the amorphous calcium phosphate used in the working examples of the instant invention may be heated, e.g., Example 1, such heating is done under conditions which explicitly retain the amorphous nature of the material, as is demonstrated by XRD analysis (Figure 3(a)).

In summary, the methods disclosed in the instant specification are distinguishable from those of Nagata and Palmer. The calcium phosphate product resulting from the instant methods is also distinguishable from the calcium phosphate product of Nagata or Palmer. In particular, Nagata and Palmer produce a highly crystalline hydroxyapatite by heating precursors to high temperature. There is no teaching or suggestion of preparing a poorly crystalline apatitic calcium phosphate having a degree of crystallinity similar to that of naturally occurring bone, as is recited in claim 1.

Niwa fails to teach the poorly crystalline apatitic calcium phosphate used in the method of the invention. Rather Niwa discloses a hydroxyapatite which is *not resorbable*. In fact, Niwa discloses the use of a hydroxyapatite in filling bone defects which acts as a porous filler which remains in the body and around which new bone grows. For example, Niwa discloses that "the growing [bone] tissue is allowed to penetrate in between the particles" (col. 7, line 57-62) and that "powder particles of the apatite calcium phosphate compound are dispersed in a newly formed bone beam" (col 8, line 25-32). Thus, Niwa teaches away from use of the poorly crystalline apatitic calcium phosphate in the method of the invention, which is required to be "strongly resorbable".

For the foregoing reasons, it is submitted that the claims 1-16 are patentable over Nagata or Palmer in view of Niwa. It is respectfully requested that the rejection be withdrawn.

**VII. Patentability of newly added claims.**

Claims 21-24 depend from claim 2, which is patentable for the reasons stated above. Claim 25 is directed to a method of embedding a prosthetic device at a bone site. Claim 26 is directed to a prosthetic device capable of embedding at a bone site. Claims 25 and 26 recite a hydrated precursor comprising ACP and a promoter, and a poorly crystalline apatitic calcium phosphate, respectively. For the reasons stated above, it is submitted that use of such materials

in a prosthetic device is not taught or suggested in the cited art. It is submitted that claims 21-26 are patentable over the art of record.

In view of the foregoing arguments, it is submitted that the claims are in condition for allowance. A favorable Notice to that effect is respectfully requested. Please charge any fees or credit any overpayments to our Deposit Account No. 03-1721.

Respectfully Submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231
on November 13, 1997